PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	
International application No. PCT/US00/20788	**Applicant's or agent's file reference** X-11072
International filing date (day/month/year) 22 August 2000 (22.08.00)	**Priority date** (day/month/year) 03 September 1999 (03.09.99)
Applicant THOR, Karl, Bruce	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 March 2001 (05.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Kiwa Mpay
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US0020788

14

PATENT COOPERATION TREATY

PCT

REC'D 23 NOV 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-11072		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/20788	22/08/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A61K31/138		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/03/2001	21.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pa l Soto, R Telephone No. +49 89 2399 7346

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/20788

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-41 as originally filed

Claims, No.:

1-54 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 24-54 (industrial applicability).

because:

   ☒ the said international application, or the said claims Nos. 24-54 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-32 and 34-54

	No:	Claims	33
Inventive step (IS)	Yes:	Claims	1-32 and 34-54
	No:	Claims	33
Industrial applicability (IA)	Yes:	Claims	1-23; for 24-54 see separate sheet
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 24-54** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the documents cited in the International Search Report according to the order of citation therein, namely:

   D1: ZA-A-9300694 (LILLY CO ELI) 3 June 1993;
   D2: M.H. BEERS AND R. BERKOW: 'The Merck Manual of Diagnosis and Therapy, Seventeenth Edition' January 1999;
   D3: WO9901132 A (GORNY PHILIPPE; REAL 2000 LIMITED (IE)) 14 January 1999;
   D4: US-A-5135947 (ROBERTSON DAVID W ET AL) 4 August 1992;
   D5: US-A-5 830 500 (RONSEN BRUCE ET AL) 3 November 1998;
   D6: MCMAHON CHRIS G ET AL, June 1999; and
   D7: PAICK J S (REPRINT) ET AL, May 1998.

3. The present application relates to:
   (i) the use of a rapid-onset selective serotonin reuptake inhibitor, or a pharmaceutically acceptable salt thereof, on an as-needed basis, for the manufacture of a medicament for treatment or management of sexual dysfunction in a mammal in need of treatment (**claim 1**),
   (ii) an article of manufacture comprising packaging material and a pharmaceutical agent effective for treating premature ejaculation in a human male comprised therein, and wherein said packaging material comprises a label as specified in **claim 19**, and wherein said pharmaceutical agent comprises a rapid-onset

selective serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof,

(iii) a method of treating or managing sexual dysfunction in a mammal which comprises administering on an as-needed basis to the mammal a therapeutically effective amount of a rapid-onset selective serotonin reuptake inhibitor (**claim 24**), and

(iv) a method of treating or managing sexual dysfunction in a mammal which comprises administering on an as-needed basis a non-rapid-onset selective serotonin reuptake inhibitor delivered in a rapid release formulation (**claim 33**).

NOVELTY

4.1. Present **claims 1-32 and 34-54** meet the requirements of the PCT with respect to novelty (Art. 33(2)). In particular, none of the documents cited in the Search Report as X documents are regarded as novelty destroying for said claims for the following reasons.

(a) **D2** (see first and second paragraphs on page 1559) discloses a method to treat premature ejaculation in men consisting in the administration of small doses of a selective serotonin reuptake inhibitor 1 or 2 hours before a sexual encounter. However, the document does not mention either dapoxetine or the requirements of a particular pharmacokinetic properties for the SSRI.

(b) **D5** (see the abstract, from column 1, line 59 to column 2, line 17; and column 3, from line 14 to 31) discloses a rapid-release composition of fluoxetine, a SSRI, for the treatment of premature ejaculation, which includes an as-needed administration thereof or precoital dose. Similarly, **D6** (see the abstract, paragraph 1 on right column on page 1826, from right column on page 1828 to left column on page 1830) discloses the treatment of premature ejaculation on an as-needed basis by administering another SSRI, paroxetine. Finally, **D7** (see the whole document) also discloses the use of a SSRIs, sertraline, for the treatment of premature ejaculation on an as-needed basis.

The technical feature in present claims 1, 19 and 24 of "rapid-onset" with the meaning specified in the 4th paragraph on page 11 of the description does not allow

a distinction of the SSRI referred to in the claims over the SSRIs addressed in **D5**, **D6** and **D7**, i.e. fluoxetine, paroxetine and sertraline, because there are no tests of the pharmacokinetic profile available for these SSRIs. However, the applicant asserts (see lines 6-10 and 19-23 on page 8 of the application) that paroxetine, fluoxetine and sertraline are non-rapid onset SSRIs.

An absolute certainty about the novelty of present claims 1, 19, 24-28 and 31-32 over **D5**, **D6** and **D7** would however require evidence that the Tmax for these SSRIs is not less than 4 hours. However, prn dosing with dapoxetine improves the ejaculatory latency after the very first dose (see lines 19-23 on page 8 of the application) and this is not achieved by any of the SSRI used in the treatments disclosed in **D5**, **D6** and **D7**. In the best of cases (see first paragraph of the discussion in **D6**), the inprovement is seen with paroxetine within 1 to 2 weeks of as-needed administration. This advantageous effect of the treatment according to the present invention supports a longer onset for paroxetine, as well as for fluoxetine and sertraline compared to dapoxetine. Consequently, in the absence of evidence showing the opposite, present claims 1-32 and 34-54 are regarded as novel over said documents.

4.2. However, present **claim 33** lacks novelty over **D5**.

INVENTIVE STEP

5. Present **claims 1-32 and 34-54** do also appear to satisfy the requirements of the PCT with respect to inventive step (Art. 33(3)). The reasons are the following.

D6, which can be considered as the closest prior art, discloses the use of paroxetine for the treatment of premature ejaculation in an as-needed basis. The study demonstrates that an as-needed administration of paroxetine alone, without an initial daily drug administration, also prolongs the ejaculatory interval, although 1 to 2 weeks of as-needed administration are necessary to improve ejaculatory control.

In the light of **D6**, the **problem** to be solved by the present application is regarded as the provision of a method to treat premature ejaculation in an as-needed basis, which does not require a previous daily treatment and which improves the ejaculatory

latency after the very first dose. The **solution** provided by the present application is the use of another SSRIs, a rapid-onset one, and more in particular, dapoxetine. This is regarded as involving as inventive step because neither **D6** nor another document of the prior art, alone or in combination, points out the pharmacokinetic profile of the SSRI being crucial to solve the problem posed and/or suggest the use of dapoxetine.

INDUSTRIAL APPLICABILITY

6.1. **Claims 19-23** meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2. For the assessment of the present **claims 1-18 and 24-54** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (as present claims 24-54), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

7. The relative term "rapid-onset" used in claims 1, 19 and 24 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the SSRI to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). The meaning of said term is only clear for the person skilled in the art by reading the explicit definition given in the description (see 4th paragraph on page 11). In order to remove the present deficiency said claims should be amended whereby the meaning can be understood from the wording of the claims alone.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/20788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/138 A61P15/00 A61K31/00 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, SCISEARCH, CANCERLIT, AIDSLINE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZA 9 300 694 A (LILLY CO ELI) 3 June 1993 (1993-06-03) page 9, paragraph 1 page 13, paragraph 3 page 16, paragraph 2 page 16, paragraph 4 -page 17, paragraph 1 ---	1-31, 34-54
X	M.H. BEERS AND R. BERKOW: "The Merck Manual of Diagnosis and Therapy, Seventeenth Edition" January 1999 (1999-01) , MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION, N.J. XP002157328	1,19, 24-28, 31-33
Y	page 1558, column 2, paragraph 7 -page 1559, column 1, paragraph 2 --- -/--	1-31, 34-42, 45-54

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2001	21/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cielen, E

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 01132 A (GORNY PHILIPPE ;REAL 2000 LIMITED (IE)) 14 January 1999 (1999-01-14) abstract page 1, line 1 - line 3 page 2, line 1 - line 13 page 2, line 22 - line 28 claims 1,6	43,44
Y	US 5 135 947 A (ROBERTSON DAVID W ET AL) 4 August 1992 (1992-08-04) cited in the application abstract column 2, line 3 - line 45 examples 27,28,36,37 column 19, line 1 - line 34 column 22, line 65 -column 23, line 10 column 23, line 46 - line 60 column 24, line 45 - line 60 claims 1,5-17,48-53	1-54
X	US 5 830 500 A (RONSEN BRUCE ET AL) 3 November 1998 (1998-11-03)	1,19, 24-28, 31-33
Y	abstract column 1, line 59 -column 2, line 17 column 3, line 14 - line 31	1-42, 45-54
X	MCMAHON CHRIS G ET AL: "Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies." JOURNAL OF UROLOGY, vol. 161, no. 6, June 1999 (1999-06), pages 1826-1830, XP000980381 ISSN: 0022-5347 cited in the application	1,19, 24-28, 31-33
Y	abstract page 1826, column 2, paragraph 1 page 1828, column 2, paragraph 2 page 1829, column 1, paragraph 3 page 1829, column 2, paragraph 4 -page 1830, column 1, paragraph 1	1-5,8,9, 11-17, 19-21, 24-31, 34-37, 40,41, 45-49, 51,52

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2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PAICK J S (REPRINT) ET AL: "Self therapy with sertraline given PRN at 5 pm in treatment of premature ejaculation" JOURNAL OF UROLOGY, (MAY 1998) VOL. 159, NO. 5, SUPP. 'S!, PP. 921-921. PUBLISHER: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436. ISSN: 0022-5347., XP000980386 cited in the application	1,19, 24-28, 31-33
Y	the whole document	1-8, 11-16, 19-21, 24-31, 34-40, 45-49,51

E	WO 00 67729 A (PENTECH PHARMACEUTICALS INC) 16 November 2000 (2000-11-16)	1,19, 24-28, 31-33
	abstract page 1, line 28 - line 30 page 3, line 2 -page 5, line 10 figures 2-4 page 7, line 25 - line 29 page 8, line 3 - line 9 page 9, line 32 -page 10, line 11 page 11, line 5 - line 9 page 12, line 3 - line 14 page 14, line 22 - line 24 page 17, line 1 - line 24 page 20, line 10 - line 22 claims 1-3,6,10,20-28	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/US 00/20788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ZA 9300694 A	03-06-1993	NONE	
WO 9901132 A	14-01-1999	FR 2765483 A	08-01-1999
		AU 8446798 A	25-01-1999
		BR 9810981 A	15-08-2000
		CN 1261798 T	02-08-2000
		EP 1001775 A	24-05-2000
US 5135947 A	04-08-1992	AT 68473 T	15-11-1991
		AU 602971 B	01-11-1990
		AU 1433588 A	13-10-1988
		CA 1329937 A	31-05-1994
		CN 88102018 A,B	26-10-1988
		CY 1658 A	14-05-1993
		DE 3865504 A	21-11-1991
		DK 188288 A	12-01-1989
		EG 18584 A	30-07-1994
		EP 0288188 A	26-10-1988
		ES 2045109 T	16-01-1994
		GR 3003267 T	17-02-1993
		HK 63992 A	28-08-1992
		HU 50316 A,B	29-01-1990
		IL 85988 A	18-08-1992
		JP 1916171 C	23-03-1995
		JP 6037443 B	18-05-1994
		JP 63258837 A	26-10-1988
		KR 9607723 B	11-06-1996
		MX 11031 A	01-11-1993
		NZ 224161 A	26-04-1990
		PT 87163 A,B	01-05-1988
		SG 67092 G	04-09-1992
		SU 1568886 A	30-05-1990
		ZA 8802418 A	27-12-1989
US 5830500 A	03-11-1998	NONE	
WO 0067729 A	16-11-2000	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 19, 24-28,31-33 relate to compounds which actually are not well-defined. The use of the definitions "a rapid-onset selective serotonin reuptake inhibitor" and "a non-rapid-onset selective reuptake inhibitor" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful search impossible.
Moreover, present claims 43-44 relate to an extremely large number of possible compounds, namely "an additional therapeutic agent for treating or managing a second, different sexual dysfunction". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible.
Consequently, the search has been restricted to the compound specifically mentioned in the claims, namely dapoxetine.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
X-11072		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 20788	22/08/2000	03/09/1999
Applicant		
ELI LILLY AND COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LENTZ, Nelson L.
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

RECEIVED
NOV 30 2001
ELI LILLY & COMPANY
PATENT DIVISION

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	21.11.2001
Applicant's or agent's file reference: X-11072	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/20788	22/08/2000	03/09/1999

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-11072		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/20788	22/08/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A61K31/138		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/03/2001	21.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pa I Soto, R Telephone No. +49 89 2399 7346

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/20788

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-41 as originally filed

Claims, No.:

1-54 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 24-54 (industrial applicability).

because:

   ☒ the said international application, or the said claims Nos. 24-54 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-32 and 34-54

	No:	Claims	33
Inventive step (IS)	Yes:	Claims	1-32 and 34-54
	No:	Claims	33
Industrial applicability (IA)	Yes:	Claims	1-23; for 24-54 see separate sheet
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 24-54** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the documents cited in the International Search Report according to the order of citation therein, namely:

   D1: ZA-A-9300694 (LILLY CO ELI) 3 June 1993;
   D2: M.H. BEERS AND R. BERKOW: 'The Merck Manual of Diagnosis and Therapy, Seventeenth Edition' January 1999;
   D3: WO9901132 A (GORNY PHILIPPE; REAL 2000 LIMITED (IE)) 14 January 1999;
   D4: US-A-5135947 (ROBERTSON DAVID W ET AL) 4 August 1992;
   D5: US-A-5 830 500 (RONSEN BRUCE ET AL) 3 November 1998;
   D6: MCMAHON CHRIS G ET AL, June 1999; and
   D7: PAICK J S (REPRINT) ET AL, May 1998.

3. The present application relates to:
   (i) the use of a rapid-onset selective serotonin reuptake inhibitor, or a pharmaceutically acceptable salt thereof, on an as-needed basis, for the manufacture of a medicament for treatment or management of sexual dysfunction in a mammal in need of treatment (**claim 1**),
   (ii) an article of manufacture comprising packaging material and a pharmaceutical agent effective for treating premature ejaculation in a human male comprised therein, and wherein said packaging material comprises a label as specified in **claim 19**, and wherein said pharmaceutical agent comprises a rapid-onset

selective serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof,

(iii) a method of treating or managing sexual dysfunction in a mammal which comprises administering on an as-needed basis to the mammal a therapeutically effective amount of a rapid-onset selective serotonin reuptake inhibitor (**claim 24**), and

(iv) a method of treating or managing sexual dysfunction in a mammal which comprises administering on an as-needed basis a non-rapid-onset selective serotonin reuptake inhibitor delivered in a rapid release formulation (**claim 33**).

NOVELTY

4.1. Present **claims 1-32 and 34-54** meet the requirements of the PCT with respect to novelty (Art. 33(2)). In particular, none of the documents cited in the Search Report as X documents are regarded as novelty destroying for said claims for the following reasons.

(a) **D2** (see first and second paragraphs on page 1559) discloses a method to treat premature ejaculation in men consisting in the administration of small doses of a selective serotonin reuptake inhibitor 1 or 2 hours before a sexual encounter. However, the document does not mention either dapoxetine or the requirements of a particular pharmacokinetic properties for the SSRI.

(b) **D5** (see the abstract, from column 1, line 59 to column 2, line 17; and column 3, from line 14 to 31) discloses a rapid-release composition of fluoxetine, a SSRI, for the treatment of premature ejaculation, which includes an as-needed administration thereof or precoital dose. Similarly, **D6** (see the abstract, paragraph 1 on right column on page 1826, from right column on page 1828 to left column on page 1830) discloses the treatment of premature ejaculation on an as-needed basis by administering another SSRI, paroxetine. Finally, **D7** (see the whole document) also discloses the use of a SSRIs, sertraline, for the treatment of premature ejaculation on an as-needed basis.

The technical feature in present claims 1, 19 and 24 of "rapid-onset" with the meaning specified in the 4th paragraph on page 11 of the description does not allow

a distinction of the SSRI referred to in the claims over the SSRIs addressed in **D5**, **D6** and **D7**, i.e. fluoxetine, paroxetine and sertraline, because there are no tests of the pharmacokinetic profile available for these SSRIs. However, the applicant asserts (see lines 6-10 and 19-23 on page 8 of the application) that paroxetine, fluoxetine and sertraline are non-rapid onset SSRIs.

An absolute certainty about the novelty of present claims 1, 19, 24-28 and 31-32 over **D5**, **D6** and **D7** would however require evidence that the Tmax for these SSRIs is not less than 4 hours. However, prn dosing with dapoxetine improves the ejaculatory latency after the very first dose (see lines 19-23 on page 8 of the application) and this is not achieved by any of the SSRI used in the treatments disclosed in **D5**, **D6** and **D7**. In the best of cases (see first paragraph of the discussion in **D6**), the inprovement is seen with paroxetine within 1 to 2 weeks of as-needed administration. This advantageous effect of the treatment according to the present invention supports a longer onset for paroxetine, as well as for fluoxetine and sertraline compared to dapoxetine. Consequently, in the absence of evidence showing the opposite, present claims 1-32 and 34-54 are regarded as novel over said documents.

4.2. However, present **claim 33** lacks novelty over **D5**.

INVENTIVE STEP

5. Present **claims 1-32 and 34-54** do also appear to satisfy the requirements of the PCT with respect to inventive step (Art. 33(3)). The reasons are the following.

D6, which can be considered as the closest prior art, discloses the use of paroxetine for the treatment of premature ejaculation in an as-needed basis. The study demonstrates that an as-needed administration of paroxetine alone, without an initial daily drug administration, also prolongs the ejaculatory interval, although 1 to 2 weeks of as-needed administration are necessary to improve ejaculatory control.

In the light of **D6**, the **problem** to be solved by the present application is regarded as the provision of a method to treat premature ejaculation in an as-needed basis, which does not require a previous daily treatment and which improves the ejaculatory

latency after the very first dose. The **solution** provided by the present application is the use of another SSRIs, a rapid-onset one, and more in particular, dapoxetine. This is regarded as involving as inventive step because neither **D6** nor another document of the prior art, alone or in combination, points out the pharmacokinetic profile of the SSRI being crucial to solve the problem posed and/or suggest the use of dapoxetine.

INDUSTRIAL APPLICABILITY

6.1. **Claims 19-23** meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2. For the assessment of the present **claims 1-18 and 24-54** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (as present claims 24-54), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

7. The relative term "rapid-onset" used in claims 1, 19 and 24 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the SSRI to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). The meaning of said term is only clear for the person skilled in the art by reading the explicit definition given in the description (see 4th paragraph on page 11). In order to remove the present deficiency said claims should be amended whereby the meaning can be understood from the wording of the claims alone.